

We claim:

1. A method for constructing a gene network, comprising the steps of:
5 (a) providing a quantitative time course data library for a set of genes of an organism, said library including expression results based on time course of expression of each gene in said set of genes, quantifying an average effect and a measure of variability of each time point on each other of said genes;

10 (b) creating a gene expression matrix from said library;
 (c) generating network relationships between said genes; and
 (d) determining if one or more groups of genes is expressed differently from
other of said groups of genes.

2. The method of claim 1, further comprising the step of:

15 (e) providing a Bayesian computational model, wherein said Bayesian model comprises minimizing a BNRC_{dynamic} criterion.

3. The method of claim 2, wherein said step of minimizing a BNRC_{dynamic} criterion comprises using a non-linear curve fitting method selected from the group consisting of polynomial bases, Fourier series, wavelet bases, regression spline bases and B-splines.

20 4. The method of claim 1, wherein said data library is created using time course study to alter gene expression.

25 5. The method of claim 2, wherein said step of minimizing said BNRC_{dynamic} criterion further comprises selecting a Bayesian mode using a backfitting algorithm.

6. The method of claim 2, wherein said step of minimizing a BNRC_{dynamic} criterion

further comprises using Akaike's information criterion.

7. The method of claim 2, wherein said step of minimizing a BNRC_{dynamic} criterion further comprising using maximum likelihood estimation.

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8. The method of claim 1, wherein said genes are associated with a cell cycle.

9. The method of claim 2, wherein said measure of variability is variance.

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10. The method of claim 3, wherein said non-linear curve fitting method is a non-parametric method.

11. The method of claim 10, wherein said non-parametric method for minimizing a BNRC_{dynamic} criterion includes using heterogeneous error variances.

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12. The method of claim 11, wherein said step of minimizing a BNRC_{dynamic} criterion further comprises the steps of:

- (1) making a score matrix whose $(i, j)^{\text{th}}$ element is the BNRC_{dynamic}^{*i* score of the graph gene_{*i*} → gene_{*j*};}
- (2) implementing one or more of add, remove and reverse which provides the smallest BNRC_{dynamic}; and
- (3) repeating step 2 until the BNRC_{dynamic} does not reduce further.

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13. The method of claim 11, wherein said step of minimizing a BNRC_{dynamic} criterion further comprises the step of applying a hill-climbing algorithm to minimize BNRC^{*i,j*_{dynamic}.}

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14. The method of claim 11, wherein an intensity of the edge is determined using a bootstrap method.

15. The method of claim 14, wherein said bootstrap method comprises the steps of:

5 (1) providing a bootstrap gene expression matrix by randomly sampling a

number of times, with replacement, from the original gene library expression data;

(2) estimating the genetic network for gene_i and gene_j;

10 (3) repeating steps (1) and (2) T times, thereby producing T genetic networks; and

(4) calculating the bootstrap edge intensity between gene_i and gene_j as
$$(t_1 + t_2)/T.$$

16. A method for elucidating a gene network, comprising the steps of:

15 (a) providing a raw data library of time-course gene expression data for a

plurality of genes of an organism;

(b) subtracting background signal intensities from said raw data library;

(c) calculating the relative change in gene expression for each of said plurality of genes;

20 (d) analyzing the statistical significance of said relative in gene expression using Student's t-test; and

(e) fitting said changes in gene expression to a linear spline function.

17. The method of claim 16, further comprising the step of removing from consideration, those genes whose expression levels are sufficiently low so as to be 25 determined predominantly by noise.

18. The method of claim 1, wherein said step of grouping comprises grouping said genes into one or more equivalence sets.

19. A method for estimating a gene network relationship, comprising the steps of:

5 (1) Making a p x p matrix whose (i,j)th element is a BNRC score of the graph

gene_i → gene_j;

(2) select a candidate set of parent genes of gene_j that gives a small BNRC score

(3) select a computational order of said parent genes;

10 (4) repeat the following steps;

(4.1) for gene_i, either add a parent gene or delete a parent gene;

(4.2) recalculate BNRC_{dynamic} score;

(4.3) repeat steps 3.1 and 3.2 until a suitable convergence criterion is satisfied;

15 (5) permute the computational order of said parent genes in step (3);

(6) repeat step (4); and

(7) repeat steps (5) and (6) until BNRC_{dynamic} is minimized.

20. A method for constructing a gene network model of a system containing a network of genes from time course gene expression data, said method comprises using a Bayesian computational model, wherein said Bayesian computational model comprises minimizing a BNRC_{dynamic} criterion.

25. The method of claim 20, wherein minimizing the BNRC_{dynamic} criterion comprises using a non-linear curve fitting method selected from the group consisting of polynomial bases, Fourier series, wavelet bases, regression spline bases and B-splines.

22. The method of claim 20, wherein minimizing the BNRC_{dynamic} criterion comprises selecting a Bayesian mode using a backfitting algorithm.

5 23. The method of claim 20, wherein minimizing the BNRC_{dynamic} criterion comprises using Akaike's information criterion.

24. The method of claim 20, wherein minimizing the BNRC_{dynamic} criterion comprises using maximum likelihood estimation.

10 25. The method of claim 20, wherein minimizing the BNRC_{dynamic} criterion comprises using a non-linear curve fitting method, wherein the non-linear curve fitting method is a non-parametric method.

15 26. The method of claim 25, wherein the non-parametric method includes using heterogeneous error variances.

27. The method of claim 26, wherein minimizing the BNRC_{dynamic} criterion further comprises the steps of:

20 (1) making a score matrix whose $(i, j)^{\text{th}}$ element is the BNRC_{dynamic}^j score of the graph gene_i → gene_j;

(2) implementing one or more of add, remove and reverse which provides the smallest BNRC_{dynamic}; and

(3) repeating step 2 until the BNRC_{dynamic} does not reduce further.

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28. The method of claim 26, wherein minimizing the BNRC_{dynamic} criterion further comprises the step of applying a hill-climbing algorithm to minimize BNRC^(j)_{dynamic}.

29. The method of claim 26, wherein an intensity of the edge is determined using a
5 bootstrap method.

30. The method of claim 29, wherein said bootstrap method comprises the steps of:

(1) providing a bootstrap gene expression matrix by randomly sampling a number of times, with replacement, from the original gene library expression data;

10 (2) estimating the genetic network for gene_i and gene_j;

(3) repeating steps (1) and (2) T times, thereby producing T genetic networks;

and

(4) calculating the bootstrap edge intensity between gene_i and gene_j as

$(t_1 + t_2)/T$.

15 31. A data file comprising a gene network model constructed by the method of claim
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32. The data file of claim 31 in a computer readable form.

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33. The data file of claim 31 accessible from a remote location.

34. The data file of claim 31 accessible from an internet web location.

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35. A method for identifying a target gene in a system containing a gene network, comprising:

(a) constructing a first and second gene network model using a Bayesian computational model,

5 wherein said Bayesian computational model comprises minimizing a BNRC_{dynamic} criterion,

wherein the first gene network model is obtained by analyzing a first gene expression profile and the second gene network model is obtained by analyzing a second gene expression profile, and

10 wherein the first gene expression profile is obtained from the system at a first time point and the second gene expression profile is obtained from the system at a second time point after said first time point, and

(b) analyzing the first and second gene network model using said Bayesian computational model, wherein the time course of gene expression is quantified, and
15 wherein a parent gene is identified as the target gene.

36. The method of claim 35, wherein the target gene is a parent gene.

37. The method of claim 35, wherein the target gene is a gene downstream from a
20 parent gene.

38. A data file containing the identity of one or more target genes obtained according to the method of claim 35.

25 39. The data file of claim 38 in a computer readable form.

40. The data file of claim 38 accessible from a remote location.

41. The data file of claim 38 accessible from an internet web location.

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42. A method of providing a service comprising

(1) receiving a data set from a party,

said data set comprising time course expression data of a group of genes;

and

10 (2) determining network relationships between genes in said group by minimizing a BNRC_{dynamic} criterion.

43. The method of claim 42, wherein receiving said data set comprises receiving the identity of at least one of said genes.

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44. A method of providing a service comprising receiving an agent from a party, and identifying a target gene for the party using the gene network model constructed according to the method of claim 35.

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